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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,461	06/12/2001	Stephen Dudley Holmes	P50186-2XC2	7066

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EXAMINER	
HUFF, SHEELA JITENDRA	

ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 04/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/879,461	HOLMES ET AL.	
	Examiner	Art Unit	
	Sheela J Huff	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed 3/3/03 has been considered and is persuasive-in-part.

The rejection of claims 17-18 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment.

The rejection of claims 1-9 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment.

All of the art rejections are withdrawn in view of applicant's amendments/arguments.

Claims 1-9 and 14-18 are pending.

Claim Rejections - 35 USC § 112

Claim 3 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The reasons for this rejection are of record in paper no. 5, mailed 9/4/02.

Applicant indicates that the deposit information is found at page 32. This sections does not contain the proper assurances. Specifically the section does not address the following part of the rejection:

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature

and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 and 17-18 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-18 and 28-29 and 34-35 of US Patent No. 5914110. The reasons for this rejection are of record in paper no. 5, mailed 9/4/02.

Applicant indicates that a terminal disclaimer will be filed when the claims are otherwise allowable.

Claim Rejections - 35 USC § 112

Claim 8 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Please note that the rejections under 35 U.S.C. 112, second paragraph, (items 7a-7h and j of paper no. 5, mailed 9/4/02) have been withdrawn in view of applicant's amendments. Only item 7i remains.

Applicant indicates that the change from leu to lys has been made. No change has been made.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating

obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Queen et al WO 90/07861 in view of Co et al Nature vol. 351 p. 501 (1991), Abrams et al US 5041381, Chreiten et al J. Immunol. Methods vol. 117 p. 67 (1991), Curtis et al US 5108910, Orlandi PNAS vol. 86 p. 3833 (1989), JP-327725, Coffman et al WO 89/06975 and Maggio Enzyme-Immunoassay CRC Press Inc. 1980 pp. 167-178.

Queen et al disclose methods for producing fusion proteins which are chimeric or CDR-grafter humanized antibodies. The reference discloses an approach to producing CDR grafter antibodies which involves the selection of human variable regions which are homologous to the murine variable region to be humanized and computer modeling to identify murine framework residues which make key contacts with CDR's, which are then introduced into human frameworks (see abstract, p 4-6 and 10-11). This reference also discloses that the art recognizes that humanized antibodies are expected to have advantages for use in vivo human therapy (page 3).

The only differences between the instant invention and the reference is the specificity of the antibody, the pharmaceutical compositions, the cloning of the immunoglobulin variable domains and the advantages of using a fusion protein linked to an additional peptide.

Co et al disclose that the art recognized that humanized antibodies were expected to have advantages for use in vivo human therapy application (page 501).

Abrams et al disclose rat monoclonal antibody 1C1.11B4.6 which has specificity for human IL-4. The authors suggest that neutralizing anti-IL-4 antibodies have potential therapeutic utility (see col. 2). Abrams further teaches of compositions containing a therapeutic amount of at least one monoclonal antibody in a pharmaceutically effective carrier. (col. 5, lines 55-60).

Curtis et al disclose advantages of an amino acid sequence of the fusion protein being linked to an additional peptide. This peptide is highly antigenic and provides an epitope reversible bound by a specific monoclonal antibody. Curtis concludes that this second fusion to the original protein is superior over the original fusion protein of Granulocyte Marcophage Colony Stimulating Factor and IL-3 alone (col. 7).

Chretien et al teach neutralizing anti-IL-4 rat mab 11B4 which has use in immunoenzymatic assay, immunopurification and potential implications in certain pathological conditions.

JP-327725 (Derwent Publ. Ltd. abstract 91-284372) teaches high affinity mouse monoclonal antibodies specific for human IL-4 which neutralize IL-4 activity and a method for detection of IL-4 comprising the steps of contacting a biological fluid with monoclonal antibody and assaying for the occurrence of binding of antibody and IL-4 (see sections 3 and 11).

Orlandi et al disclose methods using primers for V domains of mouse immunoglobulin heavy and light chains for forced cloning and amplificationof mouse hybridomas.

Maggio disclose that high affinity antibodies display affinity constants on the order of 10^{10} $(M/l)^{-1}$ to 10^{12} $(M/l)^{-1}$ resulting in sensitivities of about 10^{10} and 10^{12} M. Maggio further teaches that affinity between antigoen and antobid probably limits the sensitivity in immunoassay procedures that use the most sensitive lab-detection methods.

Coffman et al disclose blocking antibodies specific for IL-4 have potential for reducing IgE responses associated with certain human immune disorders.

In view of Orlandi et al, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to clone and sequence the hybridoma of the mouse monoclonal antibodies to IL-4 which have neutralizing activity (see secondary references). A large proportion of such antibodies would have been expected to have dissociation constant of 2×10^{-10} or less. Having obtained the murine neutralizing antibodies and cloning and sequencing them, it would have been obvious to applicant methods such as those taught by Queen et al is order to develop fusion proteins which are chimeric antibodies having murine variable regions and human constant regions of humanized antibodies comprised of mouse CDR's fused to framework sequences derived from human antibodies having variable regions with high homology to the murine antibodies to be humanized. It would have been further obvious to include a pharmaceutically acceptable carrier as taught by Abrams and to include a second fusion partner as taught by Curtis et al for the purpose of increasing the desired effects. One would have been motivated to screen for a high affinity antibody with a dissociation constant equal to or less than of 2×10^{-10} in view of the teaching by Maggio that the affinity between antigen and antibody limits the sensitivity in immunoassay procedures that use the most sensitive label-detection methods.

One of ordinary skill would have been motivated to produce the claimed antibodies and fusion proteins in view of the teaching of Coffman et al that blocking antibodies specific for IL-4 had potential for reducing IgE responses associated with

certain human immune disorders together with the recognized advantages of humanized antibodies for human therapy as characterized by Co et al. One would have been motivated to produce the claimed pharmaceutical composition for use in therapy.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J Huff whose telephone number is 703-305-7866. The examiner can normally be reached on T,Th 6am-12pm and alternate Mondays 6am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Sheela J Huff
Primary Examiner
Art Unit 1642